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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/657,076	09/09/2003	Mitsuhiro Ueno	UENO=8A	9181

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/657,076	UENO ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *1-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/743,354.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/9/03;11/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restriction

Applicant's election with traverse of Group IV, Claims 13-20, 29-33 and 40-45 in the reply filed on 7/14/06 is acknowledged. The traversal is on the ground(s) that a complete search of the elected Group IV would overlap with at least some of the other groups and there would not be a serious burden for the examiner to examine at least some of the other non-elected groups. Applicants indicate that the second paragraph of MPEP 803 requires search and examination of plural inventions if there is no serious burden on the examiner in doing so. Applicants request that the examiner reconsider the outstanding restriction requirement and examine at least some of the other groups with the elected Group IV. This is not found persuasive because a burdensome search can be shown by, for example, divergent classification of the different inventions and non-coextensive searches which would be required for the different inventions. In the instant case, the different inventions are each classified in different Class/subclasses. Also, a search of the invention of elected Group IV would not be co-extensive with a search of the other inventions. For example, the culturing conditions for the target cells in Group I would not be a part of any search of the gene therapy methods of Group IV. A search of the chemical modification methods of Group II or the functional substances that could bind retroviruses (Group III) would likewise not identify art relating to the gene therapy method of Group IV. However, applicants' arguments are persuasive with regard to the subject matter of Groups V and VI and these Groups will be examined with the elected Group IV. Claims 13-45 will be examined

The requirement is still deemed proper and is therefore made FINAL.

Substitute Specification

A substitute specification excluding the claims is required pursuant to 37 CFR 1.125(a) because the specification is not in proper idiomatic English.

A substitute specification must not contain new matter. The substitute specification must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. An accompanying clean version (without markings) and a statement that the substitute specification contains no new matter must also be supplied. Numbering the paragraphs of the specification of record is not considered a change that must be shown.

35 USC 112, 2nd Paragraph Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-20, 29-33 and 40-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13 and 14 (and dependent claims) are vague in that in step (1) applicants recite "contacting a solution containing a retrovirus with a functional substance that binds to the retrovirus **and being immobilized on a substrate** (emphasis added) for 3 hours or longer". It is unclear what is being immobilized on the substrate. It is unclear if the substance is immobilized on the substrate for 3 hours or more or if the retrovirus is contacted with the immobilized functional substance for 3 hours or more.

Claim 13 is also vague in that it recites "transplanting the cell obtained **tin** (emphasis added) step". The word "tin" should be changed to --in--.

Claim 15 is vague in that the phrase "and being immobilized on a substrate" is unclear. It is unclear if the substance is immobilized on the substrate before or after the precipitation step.

Claims 17 and 30 are vague in that there is no antecedent basis for the term "the substrate on which the functional substrate that binds to the retrovirus and another functional substrate that binds to the target cell are immobilized". There is antecedent basis for the substrate upon which the functional substance that binds the retrovirus is immobilized. Also, the claims end with the phrase "is used"; it is unclear what it is used for?

Claims 20 and 33 are vague in that "sodium butylate" appears to be incorrect. The specification provides support for "sodium butyrate".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim a method of gene therapy (*ex vivo*) wherein target cells (i.e. hematopoietic stem cells) are infected with retroviruses by contacting the cells with retroviruses bound to functional substances immobilized on substrates and the infected cells are subsequently transplanted into a recipient patient.

Initially, it is noted that the claims recite a method of gene therapy comprising infecting target cells with "retroviruses". The retroviruses are not recited as recombinant retroviruses or recombinant retroviral vectors and hence can read on wild type retroviruses. Clearly there is no enablement for a method of gene therapy using wild type retroviruses and a reading of the instant specification indicates that applicants mean to claim a gene therapy method using recombinant retroviral vectors. With respect to the instant enablement rejection, the claims will be examined as reading on gene therapy using recombinant retroviral vectors.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known

in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reaches by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following: 1) Unpredictability of the art. The gene therapy art is highly unpredictable. The unpredictability is manifested in virtually all aspects of gene therapy. The primary areas of unpredictability involve delivery of the vectors to the appropriate tissues, targeting of the vectors to the appropriate cells, the transient and unpredictable expression of the transgene in cells *in vivo* and the lack of suitable animal models of human diseases where results of potential gene therapy treatments can be extrapolated to humans. Specifically, with regard to retroviral vectors, additional problems exist with regard to random integration of the vector nucleic acid into the cellular genome with the associated possible disruption of normal genes, activation of oncogenes, transgene promoter silencing by adjacent chromosomal sequences, poor efficiency of transfection of target cells *in vivo*, poor efficiency of transduction of pseudotyped retroviral vectors *in vivo*, host immune recognition of infected cells carrying a transgene as foreign, etc. Indeed, recently all U.S. clinical studies using retroviruses as gene therapy agents were put on hold due to the possibility that retroviral vectors may result in leukemia in patients treated with retroviral vectors (See Marshall, Science, 2003, Vol. 299, No. 5605, p. 320). For reviews of the unpredictability of gene therapy techniques using retroviruses (and other viral vectors), see Mountain, TIBTECH, 2000, Vol. 18, pp. 119-128; Kmiec,

American Scientist, 1999, Vol. 87, pp. 240-247) Anderson, Nature, 1998, Vol. 392, pp. 25-30; Verma et a1., Nature, 1997, Vol. 389, pp. 239-242; Paillard, Human Gene Therapy, 1998, Vol. 9, pp. 767-768; Fox, Nature Biotechnology, 2000, Vol. 18, pp. 143-144; Goncalves, BioEssays, 2005, Vol. 27, pp. 506-517, etc.

With regard to gene therapy involving infecting hematopoietic stem cells *ex vivo*, many of the same problems which have prevented successful practicing of other aspects of gene therapy also affect this protocol. For example, Brenner et al. (Biochimica et Biophysica Acta, 2003, Vol. 1640, pp. 1-24) notes that:

> However, the biological obstacles that require solution include low rates of transduction, low protein expression, silencing of expression from the integrated vector, risk from insertional mutagenesis, and in the case of hematopoietic stem cells (HSC) the numerical disadvantage of the engrafting transduced stem cells relative to the resident stem cells. (p. 1).

Also, Hanazono et al. (Stem Cells, 2001, Vol. 19, pp. 12-123) notes that successful engraftment and repopulation of HSCs following introduction of a transgene or following infection with recombinant viral vectors *ex vivo* has been elusive in humans and that "As a matter of course, very little clinical utility has been achieved in most of the HSC gene therapy trials" (p. 13, left column).

2) State of the art. At the time of filing of the instant application, no successful gene therapy protocol had been unambiguously demonstrated to be successful. The apparent successful gene therapy achieved in several patients with X-SCID or ADA-SCID was tempered by findings that the retroviral vectors used resulted in insertional mutagenesis and development of leukemia (See Marshall, cited above and Brenner et al., cited above).

3) Number of working examples. Applicants present no working examples of the claimed invention.

4) Amount of guidance presented by applicants. Applicants present generic guidance on administering the retroviral vector producing cells to animals or humans. Applicants however present no guidance on how the skilled artisan would overcome the art recognized problems associated with successful practicing of gene therapy using retroviral vectors.

5) Nature of the invention. The invention involves one of the most complex and unpredictable areas of molecular biology/medicine; the use of viral gene therapy vectors to treat disease in humans.

6) Level of skill in the art. The level of skill in the art is high; however, given the unpredictable nature of the art, the poorly developed state of the art, the lack of guidance provided by applicants and lack of working examples, the skilled artisan would have needed to have conducted trial and error experimentation in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have needed to conduct undue and excessive experimentation in order to practice the claimed invention.

Miscellaneous

In claim 14, step (4), the word "cell" should be plural: "cells".

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVID GUZO
PRIMARY EXAMINER

David Guzo
September 23, 2006